

## WEST Search History

DATE: Thursday, February 24, 2005

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<input type="checkbox"/>	L4	19990915	0
<input type="checkbox"/>	L3	(orthokeratolog\$4 or (\$2shap\$2 with (eye? or cornea\$))) and (type VI with collagen or transglutaminase)	8
<input type="checkbox"/>	L2	(orthokeratolog\$4 or (\$2shap\$2 with (eye? or cornea))) and (type VI with collagen or transglutaminase)	7
<input type="checkbox"/>	L1	(orthokeratolog\$4 or (\$2shap\$2 with (eye? or cornea))) same (type VI with collagen or transglutaminase)	0

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Search Results - Record(s) 1 through 8 of 8 returned.

Γ 1. Document ID: US 20050026279 A1

L3: Entry 1 of 8

File: PGPB

Feb 3, 2005

DOCUMENT-IDENTIFIER: US 20050026279 A1

TITLE: Surgical grafts and methods of preparation

Detail Description Paragraph:

[0090] The extracellular matrix of the corneal stroma contains a dense network of collagen fibrils and proteoglycans arranged in an order to allow transparency for clear vision. Keratocytes, i.e., cells in the corneal stromal matrix, are dendritic in shape, form extensive intercellular contacts; and synthesize the collagens I, V, VI, and XII, and keratan sulfate-containing proteoglycans such as lumican, keratocan, and mimecan. See Birk D E, et. al., "Collagen and glycosaminoglycan synthesis in aging human keratocyte cultures," *Exp Eye Res*, 1981;32:331-9. See also Cintron C, Hong B S, "Heterogeneity of collagens in rabbit cornea: type VI collagen," *Invest Ophthalmol Vis Sci*, 1988;29:760-6; and Funderburgh J L, Conrad G W, "Isoforms of corneal keratan sulfate proteoglycan," *J Biol Chem*, 1990;265:8297-303.

Detail Description Paragraph:

[0197] 24. Cintron C, Hong B S. Heterogeneity of collagens in rabbit cornea: type VI collagen. *Invest Ophthalmol Vis Sci* 1988;29:760-6.

[Full](#) [Title](#) [Citation](#) [Front](#) [Review](#) [Classification](#) [Date](#) [Reference](#) [Sequences](#) [Attachments](#) [Claims](#) [KWIC](#) [Drawn Desc](#) [Image](#)

Γ 2. Document ID: US 20040220599 A1

L3: Entry 2 of 8

File: PGPB

Nov 4, 2004

DOCUMENT-IDENTIFIER: US 20040220599 A1

TITLE: Device for separating the epithelium layer from the surface of the cornea of an eye

Summary of Invention Paragraph:

[0002] LASIK (Laser-Assisted In Situ Keratomileusis) is a surgical procedure intended to reduce a person's dependency on glasses or contact lenses. LASIK permanently changes the shape of the cornea, the clear covering of the front of the eye, using an excimer laser. A device, called a microkeratome, is used to cut a flap in the cornea. A hinge is left at one end of this flap. The flap is folded back revealing the stroma, the middle section of the cornea. Pulses from a computer-controlled laser vaporize a portion of the stroma and the flap is replaced. It is important that the knife used during the LASIK procedure is sharp, otherwise the quality of the procedure and the healing time are poor. Additionally the knife has to be sharp in order to produce consistent and reproducible flaps. There are some complications related to the use of microkeratomes. Common complications include the creation of an irregular flap, for example, a half flap, a buttonhole, or a total cup. These complications represent irregular incisions of

the cornea, a situation that can permanently degrade visual performance.

Detail Description Paragraph:

[0050] FIG. 19 is a diagram representing a side view of the separator 14 removing the epithelial layer 16 from a Basal membrane 1900 of the eye 10. The epithelial layer 16 is made up of epithelial cells 1902. The epithelial layer 16 overlies the Basal membrane 1900. The Basal membrane 1900 is formed from a lamina densa 1904 of about 50 nm in thickness and an underlying lamina lucida 1906 of about 25 nm in thickness. The lamina densa 1906 overlies a Bowman's layer 1908. The epithelial layer 16 anchors to the Bowman's layer via a complex mesh of anchoring fibrils (type VII collagen) and anchoring plaques (type VI collagen) that interact with the lamina densa 1904 and the collagen fibrils of the Bowman's layer 1908. The Bowman's layer 1908 overlies a corneal stroma 1910.

<a href="#">Full</a>	<a href="#">Title</a>	<a href="#">Citation</a>	<a href="#">Front</a>	<a href="#">Review</a>	<a href="#">Classification</a>	<a href="#">Date</a>	<a href="#">Reference</a>	<a href="#">Sequences</a>	<a href="#">Attachments</a>	<a href="#">Claims</a>	<a href="#">KWIC</a>	<a href="#">Draw Desc</a>	<a href="#">Image</a>
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3. Document ID: US 20030157073 A1

L3: Entry 3 of 8

File: PGPB

Aug 21, 2003

DOCUMENT-IDENTIFIER: US 20030157073 A1

TITLE: Methods for pretreating a subject with apoptotic cells

Summary of Invention Paragraph:

[0258] A surgical procedure to remove the diseased part of the cornea and replace it with a similarly sized and shaped part of a healthy donor cornea.

Summary of Invention - Table CWU:

1TABLE 1 Disease Markers Associated with Autoimmune and Atopic Diseases Marker Disease (genes/antibodies/snp's) Reference Alopecia Associated genes: HLA, McDonagh et al., 27(5) areata DBQ, DR, IL-1, AIRE CLIN EXP DERMATOL mutation, MX1 405-9 (2002) MMP-9+ and CD1a+ Heffler et al., 147(2) BR cells J DERMATOL 222-9 (2002) Ankylosin HLA-B27 Khan et al., 16(4) BEST spondylitis TNF-Alpha, IL-10 PRACT RES CLIN RHEUMATOL 675-90 (2002) Seiper et al., 61 Suppl 3 ANN RHEUM DIS III8- III18 (2002) Anti- anticardiolipin (aCL) Chi 76 Suppl 2 INT J phospholipid antibody, lupus HEMATOL 47-51 (2002) syndrome anticoagulant (LA) Rand ANNU REV MED phospholipid-binding (2002) cofactors (ss2GPI) Autoimmune haplotypes HLA-A1, - Martorell et al., 60(7) Addison's B8 and DR3 NETH J MED 269-75 Disease enzymes P45oc21, (2002) P45oscc and P45oc17 Autoimmune Mitogen-stimulated Barcellini et al., 71(3) hemolytic direct antiglobulin test AM J HEMATOL 177-83 anemia (MS-DAT) (2002) red cell alloantibodies Haspl 55(4-5) ACTA MED CROATICA 149-52 (2001) Autoimmune DRB1\*0301 and Czaja et al., 47(10) DIG hepatitis DRB1\*0401 DIS SCI 2139-50 (2002) DRbeta71 position of the HLA class II molecule Behcet's Fas ligand (FasL) Wakisaka 129(2) INT disease expression ARCH ALLERGY CD1 monoclonal IMMUNOL 175-80 (2002) antibody Poulter et al., 78(2) CLIN EXP IMMUNOL 189-95 (1989) Bullous IL2, IL-4, IL-5, IFN-Giomi et al., 30(2) J pemphigoid gamma, TGF-beta DERMATOL SCI 116-28 (2002) Cardio- beta1-adrenergic Wallukat et al., 27(7) myopathy receptor; inhibitory G- HERZ 683-90 (2002) protein G (i); G-protein receptor kinase Celiac Endomysial antibodies; Vogelsang et al., 40(7) sprue-tissue-transglutaminase Z GASTROENTEROL dermatitis antibodies I-VII (2002) HLA DQ2 Holopainen et al., 48(5) GUT 696-701 (2001) Chronic TNF-alpha; IL-6 Mullington et al., 933 fatigue IgG1 and IgG3 ANN N Y ACAD SCI immune deficiency 201-10 (2001) dysfunction Patarca 933 ANN N Y syndrome ACAD SCI 185-200 (2001) (CFIDS) Chronic HNPP deletion Korn-Lubetzki et al., inflammatory CXCL9, CXCL10, 113(3) AM J MED GENET demylenating CCL3 275-8 (2002) polyneuropathy Mahad et al., 73(3) J NEUROL NEUROSURG PSYCHIATRY 320-3 (2002) Churg- eosinophil-derived Drage et al., 47(2) J AM Strauss neurotoxin (EDN); ACAD DERMATOL 209- syndrome neutrophil elastase (NE); 16 (2002) IL-5 Cicatrical Autoantigens of BPag2 Kirtschig 49(11) pemphigoid and laminin 5 HAUTARZT 818-25 (1998) CREST Antinuclear antibodies Meyer 153(3) ANN syndrome recognizing chromosomal MED INTERNE (PARIS) centromere proteins 183-8 (2002) Cold anti-red blood cell

Havouvis et al., 32(4) agglutinin autoantibody EUR J IMMUNOL 1147- disease 56 (2002) Crohn's NOD2 3020InsC D'Amato 29(11) J disease Frameshift Mutation RHEUMATOL 2470-1 99mTechnetium- (2002) labelled monoclonal anti- Bruno et al., 91(10) granulocyte antibodies ACTA PAEDIATR 1050-5 (2002) Discoid epidermal surface Kuhn et al., 146(5) BR J lupus molecules: ICAM-1, HLA- DERMATOL 801-9 (2002) DR and 27E10 Essential IgG, anti-IgG Fabrizi et al., 22(4) mixed rheumatoid factor SEMIN NEPHROL 309-18 cryo- hepatitis C virus (HCV) (2002) globulinemia infection Ferri et al., 55(1) J CLIN PATHOL 4-13 (2002) Fibromyalgia- fibromyositis Grave's S- 100 protein, epithelial Mitselou et al., 22(3) disease membrane antigen (EMA) ANTICANCER RES 1777- (CA) repeats CAR/CAL 80 (2002) and RepIN20 occurring in Chiaramonte et al., the human SEL1L gene 232(1-2) MOL CELL BIOCHEM 159-61 (2002) Guillain- CSF IgG McFarlin et al., 307(19- Barre 20) N ENG J MED 3071183-8, 1246-1250 (1982) Schliep et al., 218 J Neurol 77-96 (1978) Hashimoto's IL-6 Weetman et al., 127(2) thyroditis J ENDOCRINOL 357-61 (1990) Idiopathic truncated isoforms of Chilosi et al., 82(10) pulmonary the p63 gene (deltaN-p63 LAB INVEST 1335-45 fibrosis proteins) (2002) extracellular signal- Yoshida et al., 198(3) J regulated kinase (ERK), c- Pathol 388-96 (2002) jun N-terminal kinase (JNK), and p38 kinase (p38 MAPK) Idiopathic GPIIb/IIIa and GPIb/IX Olsson et al., 107(3-4) thrombo- THROMB RES 135-9 cytopnic (2002) purpura (ITP) IgA TGF-beta1 and Smad 2 Ruan et al., 31(4) nephropathy IL-6 ZHONGHUA BING LI XUE ZA ZHI 314-7 (2002) Harada et al., 92(4) Nephron 824-6 (2002) Insulin oxidized LDL-anti- Atchley et al., 45(11) dependent oxidized LDL complexes DIABETOLOGIA 1562-71 diabetes (2002) Juvenile three different HLA Forre et al., 31(3) arthritis loci: HLA-A, -DR/DQ SCAND J RHEUMATOL and -DP 123-8 (2002) IL-1 alpha, IL-1Ra, IL- 6, IL-10, MIF, IFN1 Lichen CD1 monoclonal Poulter et al., 78(2) planus antibody CLIN EXP IMMUNOL 189-95 (1989) Meniere's Cl(-) under beta(2)- Mithaud et al., 283(6) disease adrenergic control AM J PHYSIOL CELL PHYSIOL C1752-C1760 (2002) Mixed RNP antibodies Tan et al. 25 ARTH connective RHEUM 1271-1277 (1982) tissue Sharp 25 ARTH RHEUM disease 767-70 (1982) Multiple CSF IgG McFarlin et al., 307(19- Sclerosis IL-17 20) N ENG J MED 3071183-8, 1246-1250 (1982) Sehliep et al., 218 J Neurol 77-96 (1978) Aggarwal et al., J BIOL CHEM (2002) Myasthenia AChR binding antibody Drachman 505 ANN N gravis radioimmunoassay Y ACAD SCI 90-105 (1987) Pemphigus IgG autoantibodies Amagai et al., 51 (3) vulgaris against desmoglein3 Keio J Med 133-9 (2002) Pernicious PAI-2 Varro et al., 123(1) anemia GASTROENTEROLOGY 271-80 (2002) Polyarteritis p-ANCA; anti-MPO van Bommel et al., nodosa 13(6) EUR J INTERN MED 392 (2002) Polychondritis collagens, matrilin-1 and Hansson et al., 4(5) cartilage oligomeric matrix ARTHRITIS RES 296-301 protein (2002) Polyglandular adrenal cortex and/or Betterle et al., 23(3) syndromes steroid 21-hydroxylase ENDOCR REV 327-64 autoantibodies (2002) Polymyalgia polymorphisms of HLA- Jacobsen et al., 29(10) J rhuematica DRB1 RHEUMATOL 2148-53 (2002) Polymyositis serum surfactant protein Ihn et al., 41(11) and D (SP-D) RHEUMATOLOGY Dermato- (Oxford) 1268-72 (2002) myositis Primary lack of secondary Einstein et al., 22(5) J agamma- follicles and follicular CLIN IMMUNOL 297- globulinemia dendritic cells 305 (2002) Primary Intestinal trefoil factor Kimura et al., 36(5) biliary (ITF) HEPATOLOGY 1227-35 cirrhosis HLA-A\*0201-restricted (2002) epitope PDC-E2 165 to 174 Malsumura et al., 36 (5) HEPATOLOGY 1125-34 (2002) Psoriasis 12R-LOX Schneider et al., 68-69 NK markers and NK-T PROSTAGLANDINS cell markers OTHER LIPID MEDIAT

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawn Desc	Image
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#### 4. Document ID: US 20030139466 A1

L3: Entry 4 of 8

File: PGPB

Jul 24, 2003

DOCUMENT-IDENTIFIER: US 20030139466 A1

TITLE: Methods for pretreating a subject with extracorporeal photopheresis

#### Summary of Invention Paragraph:

[0258] A surgical procedure to remove the diseased part of the cornea and replace it with a similarly sized and shaped part of a healthy donor cornea.

Summary of Invention - Table CWU:

1 TABLE 1 Disease Markers Associated with Autoimmune and Atopic Diseases Marker Disease (genes/antibodies/snp's) Reference Alopecia areata Associated genes: HLA, McDonagh et al., DBQ, DR, IL-1, AIRE 27(5) CLIN EXP mutation, MX1 DERMATOL 405-9 MMP-9+ and CD1a+ (2002) cells Heffler et al., 147(2) BR J DERMATOL 222-9 (2002) Ankylosin spondylitis HLA-B27 Khan et al., 16 (4) TNF-Alpha, IL-10 BEST PRACT RES CLIN RHEUMATOL 675-90 (2002) Seiper et al., 61 Suppl 3 ANN RHEUM Dis III8-III18 (2002) Antiphospholipid anticardiolipin (aCL) Chi 76 Suppl 2 INT J syndrome antibody, lupus HEMATOL 47-51 anticoagulant (LA) (2002) phospholipid-binding Rand ANNU REV cofactors (ss2GPI) MED (2002) Autoimmune haplotypes HLA-A1, Martorell et al., 60(7) Addison's Disease -B8 and DR3 NETH J MED 269-75 enzymes P45oc21, (2002) P45oscc and P45oc17 Autoimmune Mitogen-stimulated Barcellini et al., 71(3) hemolytic anemia direct antiglobulin test AM J HEMATOL (MS-DAT) 177-83 (2002) red cell alloantibodies Haspi 55(4-5) ACTA MED CROATICA 149-52 (2001) Autoimmune hepatitis DRB1\*0301 and Czaja et al., 47(10) DRB1\*0401 DIG DIS SCI 2139-50 DRbeta71 position of the (2002) HLA class II molecule Behcet's disease Fas ligand (FasL) Wakisaka 129(2) INT expression ARCH ALLERGY CD1 monoclonal IMMUNOL 175-80 antibody (2002) Poulter et al., 78(2) CLIN EXP IMMUNOL 189-95 (1989) Bullous pemphigoid IL2, IL-4, IL-5, IFN- Giomi et al., 30(2) J gamma, TGF-beta DERMATOL SCI 116-28 (2002) Cardiomyopathy betal-adrenergic Wallukat et al., 27(7) receptor; inhibitory G- HERZ 683-90 (2002) protein G(i); G-protein receptor kinase Celiac sprue-dermatitis Endomysial antibodies; Vogelsang et al., 40(7) tissue-transglutaminase Z GASTRO- antibodies ENTEROL I-VII HLA DQ2 (2002) Holopainen et al., 48(5) GUT 696-701 (2001) Chronic fatigue TNF-alpha; IL-6 Mullington et al., 933 immune dysfunction IgG1 and IgG3 ANN N Y ACAD SCI syndrome (CFIDS) deficiency 201-10 (2001) Patarca 933 ANN N Y ACAD SCI 185-200 (2001) Chronic inflammatory HNPP deletion Korn-Lubetzki et al., demylenating CXCL9, CXCL10, 113(3) AM J MED polyneuropathy CCL3 GENET 275-8 (2002) Mahad et al., 73(3) J NEUROL NEUROSURG PSYCHIATRY 320-3 (2002) Churg-Strauss eosinophil-derived Drage et al., 47(2) J syndrome neurotoxin (EDN); AM ACAD neutrophil elastase (NE); DERMATOL IL-5 209-16 (2002) Cicatrical pemphigoid Autoantigens of BPag2 Kirtschig 49(11) and laminin 5 HAUTARZT 818-25 (1998) CREST syndrome Antinuclear antibodies Meyer 153(3) ANN recognizing MED INTERNE chromosomal centromere (PARIS) 183-8 (2002) proteins Cold agglutinin anti-red blood cell Havouis et al., 32(4) disease autoantibody EUR J IMMUNOL 1147-56 (2002) Crohn's disease NOD2 3020InsC D'Amato 29(11) Frameshift Mutation J RHEUMATOL 99mTechnetium-2470-1 (2002) labelled monoclonal anti- Bruno et al., 91(10) granulocyte antibodies ACTA PAEDIATR 1050.5 (2002) Discoid lupus epidermal surface Kuhn et al., 146(5) BR molecules: ICAM-1, J DERMATOL 801-9 HLA-DR and 27E10 (2002) Essential mixed IgG, anti-IgG Fabrizi et al., 22(4) cryoglobulinemia rheumatoid factor SEMIN NEPHROL hepatitis C virus (HCV) 309-18 (2002) infection Ferri et al., 55(1) J CLIN PATHOL 4-13 (2002) Fibromyalgia- fibromyositis Grave's disease S-100 protein, epithelial Mitselou et al., 22(3) membrane antigen ANTICANCER RES (EMA) 1777-80 (2002) (CA) repeats CAR/CAL Chiaromonte et al., and RepIN20 occurring in 232(1-2) MOL CELL the human SEL1L gene BIOCHEM 159-61 (2002) Guillain-Barre CSF IgG McFarlin et al., 307 (19-20) N ENG J MED 3071183-8, 1246-1250 (1982) Schliep et al., 218 J Neurol 77-96 (1978) Hashimoto's thyroditis IL-6 Weetman et al., 127(2) J ENDOCRINOL 357-61 (1990) Idiopathic pulmonary truncated isoforms of Chilosi et al., 82(10) fibrosis the p63 gene (deltaN-p63 LAB INVEST proteins) 1335-45 (2002) extracellular signal- Yoshida et al., 198(3) regulated kinase (ERK), J Pathol 388-96 c-jun N-terminal kinase (2002) (JNK), and p38 kinase (p38 MAPK) Idiopathic GPIIb/IIIa and GPIb/IX Olsson et al., 107(3-4) thrombocytopenic THROMB RES 135-9 purpura (ITP) (2002) IgA nephropathy TGF-beta1 and Smad 2 Ruan et al., 31(4) IL-6 ZHONGHUA BING LI XUE ZA ZHI 314-7 (2002) Harada et al., 92(4) Nephron 824-6 (2002) Insulin dependent oxidized LDL-anti- Atchley et al., 45(11) diabetes oxidized LDL complexes DIABETOLOGIA 1562-71 (2002) Juvenile arthritis three different HLA Forre et al., 31(3) loci: HLA-A, -DR/DQ SCAND J and -DP RHEUMATOL 123-8 IL-1 alpha, IL-1Ra, (2002) IL-6, IL-10, MIF, IFN1 Lichen planus CD1 monoclonal Poulter et al., 78(2) antibody CLIN EXP IMMUNOL 189-95 (1989) Meniere's disease Cl(-) under beta(2)- Milhaud et al., 283(6) adrenergic control AM J PHYSIOL CELL PHYSIOL C1752-C1760 (2002) Mixed connective RNP antibodies Tan et al. 25 ARTH tissue disease RHEUM 1271-1277 (1982) Sharp 25 ARTH RHEUM 767-70 (1982) Multiple Sclerosis CSF IgG McFarlin et al., 307 IL-17 (19-20) N ENG J MED 3071183-8, 1246-1250 (1982) Schliep et al., 218 J Neurol 77-96 (1978) Aggarwal et al., J BIOL CHEM (2002) Myasthenia gravis AChR binding antibody Drachman 505 ANN N radioimmunoassay Y ACAD SCI 90-105 (1987) Pemphigus vulgaris IgG autoantibodies Amagai et al., 51(3) against desmoglein3 Keio J Med 133-9 (2002) Pernicious anemia PAI-2 Varro et al., 123(1) GASTRO-ENTEROLOGY 271-80 (2002) Polyarteritis nodosa p-ANCA; anti-MPO van Bommel et al., 13(6) EUR J INTERN MED 392 (2002) Polychondritis collagens, matrilin-1 and Hansson et at., 4(5) cartilage

oligomeric ARTHRITIS RES matrix protein 296-301 (2002) Polyglandutar adrenal cortex and/or Betterle et al., 23(3) syndromes steroid 21-hydroxylase ENDOCR REV autoantibodies 327-64 (2002) Polymyalgia polymorphisms of HLA- Jacobsen et al., 29(10) rhumatica DRB1 J RHEUMATOL 2148-53 (2002) Polymyositis and serum surfactant protein Ihn et al., 41(11) Dermatomyositis D (SP-D) RHEUMATOLOGY (Oxford) 1268-72 (2002) Primary lack of secondary Einstein et al., 22(5) agammaglobulinemia follicles and follicular J CLIN IMMUNOL

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawn Desc	Image
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Γ 5. Document ID: US 20030018348 A1

L3: Entry 5 of 8

File: PGPB

Jan 23, 2003

DOCUMENT-IDENTIFIER: US 20030018348 A1

TITLE: Device for separating the epithelium layer from the surface of the cornea of an eye

Summary of Invention Paragraph:

[0002] LASIK (Laser-Assisted In Situ Keratomileusis) is a surgical procedure intended to reduce a person's dependency on glasses or contact lenses. LASIK permanently changes the shape of the cornea, the clear covering of the front of the eye, using an excimer laser. A device, called a microkeratome, is used to cut a flap in the cornea. A hinge is left at one end of this flap. The flap is folded back revealing the stroma, the middle section of the cornea. Pulses from a computer-controlled laser vaporize a portion of the stroma and the flap is replaced. It is important that the knife used during the LASIK procedure is sharp, otherwise the quality of the procedure and the healing time are poor. Additionally the knife has to be sharp in order to produce consistent and reproducible flaps. There are some complications related to the use of microkeratomes. Common complications include the creation of an irregular flap, for example, a half flap, a buttonhole, or a total cup. These complications represent irregular incisions of the cornea, a situation that can permanently degrade visual performance.

Detail Description Paragraph:

[0051] FIG. 19 is a diagram representing a side view of the separator 14 removing the epithelial layer 16 from a Basal membrane 1900 of the eye 10. The epithelial layer 16 is made up of epithelial cells 1902. The epithelial layer 16 overlies the Basal membrane 1900. The Basal membrane 1900 is formed from a lamina densa 1904 of about 50 nm in thickness and an underlying lamina lucida 1906 of about 25 nm in thickness. The lamina densa 1906 overlies a Bowman's layer 1908. The epithelial layer 16 anchors to the Bowman's layer via a complex mesh of anchoring fibrils (type VI collagen) and anchoring plaques (type VI collagen) that interact with the lamina densa 1904 and the collagen fibrils of the Bowman's layer 1908. The Bowman's layer 1908 overlies a corneal stroma 1910.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawn Desc	Image
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Γ 6. Document ID: US 20020102581 A1

L3: Entry 6 of 8

File: PGPB

Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020102581 A1

TITLE: Diagnostics and therapeutics for ocular disorders

Summary of Invention Paragraph:

[0021] Ishibashi et al. (1986) observed cellular extensions of the RPE that protruded through the RPE basal lamina and into Bruch's membrane in eyes that were surgically enucleated for melanoma, suggesting that drusen possess, and may be derived from, RPE cell constituents. However, it should be noted that changes in RPE cytoskeletal organization and cell shape have been described in eyes with choroidal melanoma (Wallow an Tso, 1972; Fuchs, et al., 1991), making it difficult to draw conclusions about the derivation of drusen during normal senescence from these studies. Duvall et al. (1985) suggested a role for choroidal pericytes in keeping Bruch's membrane clear of debris. They suggested that dysfunction of pericytes leads to the formation of drusen, either by the accumulation of material from the choroid or by the failure to remove material deposited by the RPE. Penfold et al. (1986) have suggested a role for giant cells and mononuclear phagocytes in the pathology of the atrophic form of senile macular degeneration (see also Dastgheib and Green, 1994).

Detail Description Paragraph:

[0047] Examples of genotypic DRAMs include mutant genes and the encoded mutant polypeptide, abnormal expression of proteins, abnormal levels of expressed gene products (including mRNA or protein levels that are upregulated or downregulated), and/or a distinct pattern of differential gene expression in drusen forming ocular tissues. Markers expressed by dysfunctional and/or dying RPE cells include HLA-DR, CD68, vitronectin, apolipoprotein E, clusterin, and S-100. Markers expressed by choroidal and RPE cells in AMD include heat shock protein 70, death protein, proteasome, Cu/Zn superoxide dismutase, cathepsins, and death adaptor protein RAIDD. Markers involved in immune mediated events are associated with drusen formation include: autoantibodies, leukocytes, dendritic cells, myofibroblasts, type VI collagen, chemokines, and cytokines.

Detail Description Paragraph:

[0100] In one aspect, the invention provides a method for diagnosing, or determining a predisposition to developing a drusen associated disease by detecting one or more markers which are associated with drusen development. Examples of phenotypic markers include: RPE dysfunction and/or death, immune mediated events at the RPE-Bruch's membrane-choroid interface, dendritic cell activation, migration and differentiation, extrusion of the dendritic cell process into the sub RPE space (e.g. by detecting the presence or level of a dendritic cell marker such as CD68, CD1a and S100), and the presence of geographic atrophy or disciform scars. Examples of genotypic markers include mutant genes and/or a distinct pattern of differential gene expression ("Drusen Development Pathway"), including genes that are upregulated or downregulated in drusen forming ocular tissue associated with drusen biogenesis. For example genes expressed by dysfunctional and/or dying RPE cells include: HLA-DR, CD68, vitronectin, apolipoprotein E, clusterin and S-100. Genes expressed by choroidal and RPE cells in AMD include heat shock protein 70, death protein, proteasome, Cu/Zn superoxide dismutase, cathepsins, and death adaptor protein RAIDD. Markers involved in immune mediated events associated with drusen formation include: autoantibodies (e.g. directed against drusen, RPE and/or retina components), leukocytes, dendritic cells, type VI collagen, and a cadre of chemokines and cytokines. Molecules associated with drusen include: immunoglobulins, amyloid A, amyloid P component, HLA-DR, fibrinogen, Factor X, prothrombin, complements 3, 5, 9, and 5b-9, C reactive protein (CRP) apolipoprotein A, apolipoprotein E, antichymotrypsin, .beta.2 microglobulin, thrombospondin, and vitronectin. Markers of drusen associated dendritic cells include: CD1a, CD4, CD14, CD68, CD83, CD86, and CD45, PECAM, MMP14, ubiquitin, and FGF. Important dendritic cell-associated accessory molecules that participate in T cell recognition include ICAM-1, LFA1, LFA3, and B7, IL-1, IL-6, IL-12, TNF-alpha, GM-CSF and heat shock proteins. Markers associated with dendritic cell expression include: colony stimulating factor, TNF.alpha., and IL-1. Markers associated with dendritic cell proliferation include: GM-CSF, IL-4, IL-3, SCF, FLT-3 and TNF.alpha.. Markers associated with dendritic cell differentiation include IL-10, M-CSF, IL-6 and IL-4.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawn Desc	Image
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## 7. Document ID: US 6656705 B1

L3: Entry 7 of 8

File: USPT

Dec 2, 2003

DOCUMENT-IDENTIFIER: US 6656705 B1

TITLE: Sciellin and uses thereof

Brief Summary Text (2):

The cornified envelope is a fifteen (15) nm thick insoluble protein layer that is formed under the plasma membrane in the upper layers of epidermis and keratinizing stratified epithelium (Reichert, U. et al. (1993) Molecular Biology of the Skin, 107-150). It appears to play a major role in the physical barrier properties of the stratum corneum (Elias, P. M. and D. S. Friend (1975) J. Cell. Biol. 65:180-191). The envelope is formed from several precursor proteins by the calcium dependent enzyme transglutaminase, which catalyzes formation of .epsilon.-(.gamma.-glutamyl) lysine crosslinks (Polakowska, R. R. and L. A. Goldsmith (1991) Physiology, Biochemistry and Molecular Biology of the Skin, 168-201) that are resistant to proteolytic digestion. It has been postulated that crosslinking of an envelope related protein, involucrin, to the plasma membrane is a first step in envelope assembly (Ishida-Yamamoto, A. et al. (1997) J. Invest. Dermatol. 108:12-16). This is followed by crosslinking of the less abundant precursors such as SPRR proteins, elafin, envoplakin, filaggrin, keratin filaments and cystatin a (Steinert, P. M. and L. N. Marekov (1995) J. Biol. Chem. 270:17702-17711; Takahashi, H. et al. (1997) J. Invest. Dermatol. 108:843-847; Ruhrberg, C. et al. (1996) J. Cell. Biol. 134:715-729; Takahashi, M. et al. (1996) Arch. Biochem. and Biophys. 329:123-126). Finally loricrin covers the cytoplasmic side of the envelope (Candi, E. et al. (1995) J. Biol. Chem. 270: 26382-26390).

Brief Summary Text (4):

Gene mutation and knockout studies have been used to gather information on the function of epidermal proteins, with the keratins being the most well known (Fuchs, E. et al. (1992) PNAS 89:6906-6910; Vassar, R. et al. (1991) Cell 64:365-380). Only one study of envelope related proteins has been reported, a loricrin knockout mouse (deviragh, P. A. et al. (1996) J. Invest. Dermatol. 106:844; deviragh, P. A. et al. (1997) J. Invest. Dermatol. 108:555). Heterozygous mice are normal, while homozygotes have abnormal skin during the first few days, but the animals appear normal as adults. However, the mice have a defect in barrier function and respond abnormally to the application of some chemicals. A mutation of the loricrin gene has been observed in patients with a rare autosomal dominant palmoplantar keratoderma, Vohwinkel's Keratoderma, as well as in Progressive, Symmetric Erythrokeratoderma (Ishida-Yamamoto, A. et al. (1997) J. Invest. Dermatol. 108:12-16). Loss of epidermal transglutaminase activity from mutations in the gene results in the human disease, lamellar ichthyosis, which is characterized by a thickened stratum corneum, disturbed epidermal keratinization and inflammatory changes (Huber, M. et al. (1995) Science 267:525-528).

Brief Summary Text (30):

In a preferred embodiment, the recombinant sciellin polypeptide has one or more of the following characteristics: (i) it has the ability to form homotrimeric beta helices; (ii) it acts as a precursor of the cornified envelope of keratinizing tissues; (iii) it provides structural support to the cornified envelopes of stratum corneum cells; (iv) it promotes adhesion between tissue elements; (v) it promotes intracellular signalling; (vi) it defines cell shape; (vii) it can act as an adaptor element to promote the assembly and targeting of multiprotein complexes; (viii) it has a molecular weight, amino acid composition or other physical characteristic of sciellin of SEQ ID NO:2; (ix) it has an overall sequence similarity of at least 50%, preferably at least 60%, more preferably at least 70, 80, 90, or 95%, with a sciellin polypeptide of SEQ ID NO:2; (x) it is found in human placenta; (xi) it has a central domain composed of repeats which is preferably about 70%, 80%, 90% or 95% identical to amino acid residues 231-543 of SEQ ID NO:2; (xii) it has a carboxyl domain containing a single LIM domain which is preferably about 70%, 80%, 90% or 95% identical to amino acid residues 600-662

of SEQ ID NO:2; (xiii) it has a pI of about 10; (xiv) it can be expressed in the stratum granulosum of human foreskin tissue; and (xv) it can be expressed in the peripheral cytoplasm in hair follicles, upper cell layer of epidermis, as well as the epithelium of the oral cavity, esophagus, vagina, ureter and cornea.

Detailed Description Text (21):

The hydrophobic stretches are 5-7 residues long. and are predicted to form beta sheets. This is very similar to the parallel beta helix structure which has been described for the P22 tailspike protein and pectate lyase C (Yoder, M.D. et al (1993) *Science* 260:1503-1507). The crystal structure of the P22 tailspike protein demonstrates that each subunit of the homotrimer contains a large parallel beta helix. The beta helix of each strand is formed by short parallel beta sheets coiled into a large right-handed helix, similar to a rope coiled into a tidy cylinder. Each turn of the beta helix is comprised of between 16 and 22 residues. The hydrophobic side chains stack into the helix interior so the beta strands are arranged in stacks like rungs on a ladder. The charged and polar residues form a hydrophilic interface between adjacent beta helices in the homotrimer. The carboxyl domain of P22 tailspike protein is important for the association of monomers. By analogy, sciellin could form homotrimeric beta helices which become cross-linked by transglutaminase into very rigid protein girders, lending structural support to the cornified envelopes of stratum corneum cells. The presence of a PEST sequence could ensure that monomeric sciellin is rapidly degraded in the absence of crosslinking transglutaminases.

Detailed Description Text (22):

The repeats surrounding the amino acids LIKV were found in the repeat region of sciellin as shown in FIG. 3. The repeats involving G were few and short and NQG was found three times and GQS twice. However, the repeat IGQDPVK reported as a transglutaminase substrate in elaphin and the repeats AQEPVK and GQDKVK found to link elaphin to loricrin were not observed in sciellin. Also the sequence around glutamine 496 (EQQV) in involucrin, the preferential site of labeling by transglutaminase was not present in sciellin.

Full	Title	Citation	Front	Review	Classification	Date	Reference	...	...	...	...	...	...	...	Claims	KWIC	Draw Desc	Image
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8. Document ID: US 6218360 B1

L3: Entry 8 of 8

File: USPT

Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218360 B1

TITLE: Collagen based biomaterials and methods of preparation and use

Abstract Text (1):

This invention comprises purified native state Type VI collagen/.beta.1g, Type VI-.beta.1g collagen gel, including the crosslinked gel, and the use of the gel in fibrosis limited wound healing, and methods of preparation of the collagens.

Brief Summary Text (2):

This invention comprises purified native state Type VI collagen/.beta.1g, Type VI-.beta.1g collagen gel, including the crosslinked gel, and the use of said gel to limit fibrosis during wound healing, and methods of preparation of said collagens and gels.

Brief Summary Text (4):

Type VI collagen, a ubiquitous filamentous structural protein, is an integral component of the interfibrillar matrix, and represents a significant fraction of the connective tissue collagens. A sequence listing of one form of Type VI collagen is found in *Structure and Function of Collagen Types*, Eds. Richard Mayne and Robert E. Burgeson, (Academic Press, New York City (1987)), the teachings of which are incorporated herein by reference. Glutaraldehyde

crosslinked Type IV collagen, used as a synthetic epikeratoplasty in monkey is degraded by endogenous enzymes and fails to support a healthy epithelium. (Thompson K P, Hanna K D, Gipson I K, Gravagna P, Waring III G O, Johnson-Wint B., "Synthetic epikeratoplasty in Rhesus monkeys with human type IV collagen," Cornea. 1993;12:35-45).

Brief Summary Text (5):

Type VI collagen is one of the earliest matrix proteins deposited during cell infiltration within a collagen tissue polymer composite used to repair an abdominal wall defect. Type VI collagen is a heterotrimer composed of polypeptides .alpha.1(VI), .alpha.2(VI), and .alpha.3(VI). Each polypeptide contains globular domains at the amino and carboxyl termini separated by a short triple-helical domain. The dumbbell-shaped monomers assemble into tetramers by lateral association. End-to-end association of these tetramers forms a beaded filamentous structure.

Brief Summary Text (6):

Type VI collagen is arranged as a beaded filament with about 100 nm periods between beads. Type VI collagen is involved in cell-matrix interactions, and believed to interact with extracellular matrix components including collagens, hyaluronan, and proteoglycans. Without being bound by any particular theory, it is believed that as a structural protein, Type VI collagen plays a role in anchoring basal-lamina-containing organs within connective tissues and restricting lateral movement of collagen fibrils.

Brief Summary Text (7):

Native Type VI collagen co-purifies with a protein identified as .beta.ig-h3, a protein induced in a human adenocarcinoma cell line after treatment with TGF-.beta.. This protein in rabbit is termed .beta.ig, and is synthesized in corneal stroma during morphogenesis of normal and healing tissue, indicating that it plays a role in these processes. The 683 amino acids sequence of .beta.ig has similarity with the protein fasciclin I, a possible surface recognition molecule involved in nerve growth cone guidance, and OSF-2, a protein that has been suggested to function as an adhesion molecule in bone formation.

Brief Summary Text (8):

In corneal stroma, .beta.ig is associated with the globular domain of native Type VI collagen. This association involves disulfide-dependent linkages. A denatured Type VI collagen preparation containing .beta.ig was reported as promoting adhesion and spreading of corneal fibroblasts and smooth muscle cells in vitro. Adhesion of cells to Type VI collagen and subsequent cell spreading may be partially mediated by .beta.ig. As an integral component of the stromal interfibrillar matrix during morphogenesis, .beta.ig plays a role in development of an ordered fibrillar matrix. Without being bound by any specific theory, it is believed that such order is necessary for corneal transparency.

Brief Summary Text (9):

We have now, surprisingly, established that corneal Type VI collagen/.beta.ig is efficiently extracted without denaturation by means of phosphate buffered saline. The purified preparation, containing Type VI collagen associated with .beta.ig forms a viscous substance, which, when concentrated, is in the form of a gel termed "gelsix." We have further discovered that upon chemical crosslinking with polyethylene glycol the gel becomes a transparent film or shaped object. The crosslinked gel is termed "cxgelsix." Cxgelsix is mechanically strong enough to present a useful biomaterial in corneal and other applications.

Drawing Description Text (2):

FIG. 1a is a rotary shadowing electron micrograph of purified PBS-extracted type VI collagen preparation.

Drawing Description Text (3):

FIG. 1b is a rotary shadowing electron micrograph of purified PBS-extracted type VI collagen preparation mixed with antibodies specific to .beta.ig.

Drawing Description Text (4):

FIG. 2a is an electron micrograph of purified PBS-extracted type VI collagen/.beta.ig preparation concentrated on an Amicon filter as gelsix.

Drawing Description Text (5):

FIG. 2b is an electron micrograph of purified PBS-extracted type VI collagen/.beta.ig preparation upon incubation of the gelsix mat of FIG. 2a with acid ATP.

Drawing Description Text (6):

FIG. 3 is a hypothetical model of type VI collagen/.beta.ig. The stoichiometry of .beta.ig to Type VI collagen is believed variable.

Detailed Description Text (2):

Type VI collagen, by virtue of its distribution in corneal stroma, its synthesis during morphogenesis, and its interaction with both corneal stromal cells and extracellular matrix proteins, plays an important role in assembling and maintaining proper collagen fibril spacing so necessary for corneal transparency. As an integral component of the stromal interfibrillar matrix during morphogenesis, .beta.ig plays a role in development of an ordered fibrillar matrix. Without being bound by any specific theory, it is believed that such order is necessary for corneal transparency.

Detailed Description Text (3):

This invention comprises a purified preparation of Type VI collagen/.beta.ig in native state configuration. The invention further comprises a method of preparing purified Type VI collagen/.beta.ig in native state configuration comprising the step extracting particularized corneal stroma with substantially isotonic saline in the absence of denaturing extractants. A useful non-denaturing extractant is phosphate buffered saline, optionally in association with a protease inhibitory amount of protease inhibitor.

Detailed Description Text (4):

The invention further comprises Type VI collagen/.beta.ig gel. In one embodiment the gel is prepared from Type VI collagen/.beta.ig comprising Type VI collagen in native state configuration, and in another embodiment the gel is prepared from collagen comprising denatured Type VI collagen/.beta.ig.

Detailed Description Text (5):

The invention yet further comprises a method of preparing Type VI collagen/.beta.ig gel comprising the steps of

Detailed Description Text (6):

(a) preparing a solution of the purified Type VI collagen;

Detailed Description Text (7):

(b) centrifuging said solution on a centrifugation concentrator filter until a meniscus of Type VI collagen/.beta.ig gel is formed on said filter.

Detailed Description Text (8):

Particular note is made of Type VI collagen/.beta.ig gel in the form of a crosslinked gel termed "cxgelsix." In one embodiment cxgelsix is prepared by the step of exposing gelsix to a crosslinking effective amount of crosslinking agent. Cxgelsix is understood to be formed either from native state Type VI collagen/.beta.ig or to from denatured Type VI/.beta.ig collagen or combinations of the two with or without additional ingredients. In one embodiment of this method, the crosslinking agent is disuccinimidyl glutarate polyethyleneglycol, and optionally wherein the crosslinking effective amount is at least about 10:1 crosslinking agent to gelsix (w/w). The product of this process is particularly contemplated within this invention.

Detailed Description Text (20):

A. "Type VI collagen" shall mean the tetramer composed of the heterotrimer of polypeptides .alpha.1(VI), .alpha.2(VI) and .alpha.3(VI) as described in Structure and Function of Collagen Types, Eds. Richard Mayne and Robert E. Burgeson, (Academic Press, New York City (1987)). The heterotrimer is characterized by linear regions of about 100 to about 105 nm ending in globular portions.

Detailed Description Text (21):

B. "Native state configuration" in reference to Type VI collagen/.beta.ig shall mean that the collagen retains the ability to form bundles of Type VI collagen tetramers, 100 nm periodic fibrils ("crystallites") in the presence of ATP as shown in FIG. 2. Note that proteins are termed purified by negative testing--no contaminants found under test conditions. Type VI collagen/.beta.ig will be understood to be "purified" Type VI collagen/.beta.ig when it presents as substantially a single peak eluted on S-1000 gel at 280 nm near the void volume. Alternatively, purity of Type VI collagen/.beta.ig fractions was assessed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Purified Type VI collagen/.beta.ig was chromatographed on Sephadex S-1000, eluted with SDS/borate buffer, and the eluate assayed for Type VI collagen/.beta.ig by SDS-PAGE.

Detailed Description Text (22):

Native state Type VI collagen/.beta.ig is prepared in absence of denaturing extractants. By way of example, denatured Type VI collagen/.beta.ig was extracted from rabbit corneas with 6 M urea in the presence of iodoacetamide or N-ethylmaleimide. The urea extract was precipitated with ammonium sulfate, redissolved in sodium borate buffer, dialyzed, centrifuged, and chromatographed on a Sepharose CL-4B column. Upon re-suspension the collagen partially renatures as demonstrated by ultracentrifugation analysis.

Detailed Description Text (23):

Urea based extractions denature Type VI collagen but do not separate .beta.ig which is covalently linked by sulfhydryl linkages. These can be broken by such reagents as beta mercapto ethanol and dithiothreitol (DTT).

Detailed Description Text (25):

D. "Salt" relevant to solutions for the extraction of Type VI collagen/.beta.ig in native state configuration shall mean sodium, potassium or calcium, with particular TO reference to phosphate buffered saline, and specifically isotonic phosphate buffered saline.

Detailed Description Text (28):

D. Gel shall mean the viscous state in which most collagen is found in vivo. Gelsix is a transparent gel of Type VI collagen in association with .beta.ig. In some instances the Type VI component of gelsix is a denatured Type VI collagen, and in some instances it is in native state configuration or combinations of native state configuration and denatured states. Gelsix is a gel that can be mounded up several millimeters on a filter paper. It exhibits elasticity and retains some shape but cannot be picked up with a tweezers in a bolus. The gel is viscoelastic, and as such exists as a gel solution, a fluid which resists flow by nature of high viscosity. These fluids are elastic because they have a "memory." They return to approximately their original shape after stretch. In many instances, these solutions are optically clear and are basically aqueous solutions of higher molecular weight polymers in the molecular weight range of from at least about 2,000,000 Daltons.

Detailed Description Text (30):

F. Cxgelsix is crosslinked Type VI collagen and .beta.ig. In cxgelsix, "crosslinking" shall mean collagen molecules linked by covalent bonds to polyfunctional (including difunctional) polymers. Cxgelsix is inclusive of crosslinked gel derived from gelsix with its origin in native state Type VI collagen, but also from denatured Type VI collagen and combinations of native state and denatured. In general, crosslinking is accomplished in a substantial excess of crosslinking agent. For example 1.5 mg of gelsix exposed to a 50 mg/ml solution of succinimidyl glutarate polyethyleneglycol at 30:1 crosslinking agent to gel is such a substantial excess. Crosslinking is complete in a matter of about one to several minutes. Cxgelsix is firm and rubbery and is firm enough to be held in place by sutures. Cxgelsix is also characterized by sufficient CO<sub>2</sub> and O<sub>2</sub> transport to maintain ophthalmic tissues covered by preparations several .mu.m thickness. It is a particular advantage of cxgelsix, that in situ, such as when embedded intrastromally, it does not display a clinically adverse affect on surrounding, here, corneal tissues, and remains intact in the presence of an acute inflammatory reaction during (corneal) wound healing.

Detailed Description Text (31):

It is to be particularly understood that Type VI collagen (native state and denatured) also forms a gel in the absence of .beta.ig which is usefully crosslinked.

Detailed Description Text (41):

Type VI collagen/.beta.ig-Purification

Detailed Description Text (42):

Type VI collagen/.beta.ig from the rabbit cornea was extracted, purified, and prepared as a gel by a non-denaturing method. Details of the extraction and purification of Type VI collagen/.beta.ig are as follows:

Detailed Description Text (43):

Corneal stromas obtained from rabbit corneas (PelFreez, Rogers, Ark.) were frozen and pulverized in a Wiley mill. Powdered corneal stroma was extracted several times with phosphate buffered saline (PBS), pH 7.0 containing a protease inhibitor cocktail. The extracts were pooled, filtered, and concentrated on an Amicon diafiltration with a YM10 filter (Amicon Inc. Beverly, Mass.). The concentrate was centrifuged, and the pellet discarded. The supernatant was then put through a CL2B (Sigma, St. Louis, Mo.) column, and eluted with PBS containing 0.02% sodium azide. The eluate was monitored spectrophotometrically at 280 nm, and Type VI collagen/.beta.ig eluted near the void volume followed by a broad peak of lower-molecular-weight material. Fractions containing Type VI collagen/.beta.ig were pooled, concentrated, and recycled through the gel filtration column two additional times. The PBS extract was concentrated by ultrafiltration, and chromatographed on a CL-2B column. Purity of Type VI collagen/.beta.ig fractions were assessed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Purified Type VI collagen was chromatographed on Sephadryl S-1000, eluted with SDS/borate buffer, and the eluate assayed for Type VI collagen and .beta.ig by SDS-PAGE. Mono-specific rabbit polyclonal antibodies to .beta.ig were used for immunocytochemical analyses of human fetal corneas. Adenosine triphosphateinduced crystallite formation and immunogold analysis of the Type VI collagen/.beta.ig preparation was used to confirm identification of the purified PBS extract. Immunochemical analysis of the purified Type VI collagen preparation was conducted by rotary shadowing.

Detailed Description Text (44):

FIG. 1a is a rotary shadowing electron micrograph of purified PBS-extracted Type VI collagen preparation. The sample was incubated with non-immune serum shows the characteristic beaded filaments. The filaments of Type VI collagen (1) are composed of discrete dumbbell-like units associated end to end (2). Small unknown spherical structures associated with the globular domains (4) of Type VI collagen are evident (4). Bars=100 nm.

Detailed Description Text (45):

FIG. 1b is a rotary shadowing electron micrograph of purified PBS-extracted Type VI collagen preparation. Type VI collagen preparation was incubated with antibody against .beta.ig (anti-.beta.ig). It shows filaments of Type VI collagen (1). Irregularly enlarged globular structures (10) are the association of anti-.beta.ig with some of the globular domains of Type VI collagen. Bars=100 nm.

Detailed Description Text (46):

FIG. 2a is an electron micrograph of purified PBS-extracted Type VI collagen/.beta.ig preparation concentrated on an Amicon filter as gelsix. Type VI collagen appears as an aggregate of a mat of filaments uniformly distributed. Bar=100 nm.

Detailed Description Text (47):

FIG. 2b is an electron micrograph of purified PBS-extracted Type VI collagen/.beta.ig preparation upon incubation of the gelsix mat of FIG. 2a with acid ATP. The filaments (12) of Type VI collagen in native state configuration are converted to a highly organized ladder-like structure (18) characteristic of Type VI collagen. Immuno-gold labeling (16) of the ladder-like structure with antibody specific to Type VI collagen at the globular domain (14) indicates this structure is composed of Type VI collagen. Bar=100 nm.

Detailed Description Text (48):

FIG. 3 is a hypothetical model of type VI collagen/.beta.ig. The stoichiometry of .beta.ig to Type VI collagen is believed variable. A tetrad of Type VI collagen fibrils (22) are arranged in parallel as shown. The .beta.ig (24) is associated with the globular domains (26) of the Type VI collagen alpha polypeptides. Although the figure shows one molecule of .beta.ig-associated with each globular domain, the stoichiometry varies in specific instances.

Detailed Description Text (51):

Approximately 0.15 mg of purified Type VI collagen/pig was placed in a Centricon concentrator (Amicon, Beverly, Mass.) and centrifuged in a swinging bucket at 5000.times.g for approximately 1 hour, depending on the initial volume of the sample, until a meniscus was formed on the filter of the concentrator. The resulting product was gelsix. FIG. 2a.

Detailed Description Text (55):

Discs of cxgelsix, 2.0 and 4.0 mm in diameter, were cut out from the gel with a trephine. Stained cxgelsix, sterilized with sodium azide during isolation and purification of Type VI collagen, was extensively washed in sterile PBS, pH 7.2, and kept in 3 ml of sterile PBS containing 6 drop of 0.3% Ciprofloxacin HCl eyedrop (Alcon Laboratories, Inc, Fort Worth, Tex.) for at least one hour, followed by UV exposure for 15 minutes in a tissue culture hood to ensure sterility prior to implantation in the corneas. The cxgelsix discs implanted in corneas ranged in thickness of from 9 to 35 .mu.m, as determined by electron microscopy. In a separate preparation, the water content of the gel was determined to be approximately 87% by weight.

Detailed Description Text (76):

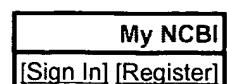
The apparent resistance of cxgelsix to degradation by endogenous enzymes is useful for anchorage of prosthetic devices to living tissues, such as corneal prostheses. By virtue of its role as a substrate for fibroblasts, and resistance to rapid degradation, chemical crosslinking of gelsix in vivo is usefully employed in a method of in situ formation of biological glue for healing wounds. In particular embodiments, crosslinks are further formed between Type VI collagen and collagens at the cut edge of the wound, as well as between Type VI filaments.

Detailed Description Text (85):

FIG. 6 is a diagrammatic



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